



Clinical trial results: The effect of melatonin on nocturnal enuresis Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2011-004138-33 |
| Trial protocol | DK |
| Global end of trial date | 06 May 2019 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 13 May 2021 |
| First version publication date | 13 May 2021 |
| Summary attachment (see zip file) | Supplementary info EudraCT 2011-004138-33 (Supplementary info EudraCT 2011-004138-33.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | EnuMel-11 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01575678 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Aarhus University Hospital |
| Sponsor organisation address | Palle Juul Jensen Boulevard 99, Aarhus N, Denmark, 8200 |
| Public contact | Britt Borg, Aarhus University Hospital, 0045 22740973, bborg@clin.au.dk |
| Scientific contact | Britt Borg, Aarhus University Hospital, 0045 22740973, bborg@clin.au.dk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 12 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 06 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 May 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of melatonin in fixed dosage before bedtime in children with monosymptomatic nocturnal enuresis on the number of wet nights per week compared with placebo.

Protection of trial subjects:

Blood- and urinesamples obtained at every follow up to monitor adverse events

Background therapy:

none

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 03 October 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 20 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 20 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 16 |
| Adolescents (12-17 years) | 4 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

All subject recruited from the outpatient clinic Center for Child Incontinence, Pediatric Department, Aarhus University Hospital

Pre-assignment

Screening details:

Patients from Centre for Child Incontinence was screened bases on their previous hospital records. If records were in accordance with inclusion and exclusion criteria, the patient was screened in person by investigators.

Number of screenet patients: 69

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor |

Blinding implementation details:

active and placebo tablets were encapsulated in in grey DB Caps(R) size B

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | No |
| Arm title | Melatonin (Circadin, Neurim 2mg) |

Arm description:

Subjects receives treatment with Melatonin (Circadin, Neurim 2mg) every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially

| | |
|--|---------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Circadin |
| Investigational medicinal product code | N05CH01o |
| Other name | |
| Pharmaceutical forms | Prolonged-release capsule |
| Routes of administration | Oral use |

Dosage and administration details:

2 mg once every evening for four weeks

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received treatment with placebo every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet once every evening for four weeks

| Number of subjects in period 1 | Melatonin (Circadin, Neurim 2mg) | Placebo |
|---------------------------------------|-------------------------------------|---------|
| Started | 20 | 20 |
| Completed | 18 | 18 |
| Not completed | 2 | 2 |
| Consent withdrawn by subject | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|------------------------------|---------------|
| Reporting group title | Overall trial |
| Reporting group description: | |
| Correction: n=20 | |

| Reporting group values | Overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 20 | 20 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 16 | 16 | |
| Adolescents (12-17 years) | 4 | 4 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 9.70 | | |
| standard deviation | ± 1.69 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 3 | |
| Male | 17 | 17 | |
| Previous desmopressin treatment | | | |
| Units: Subjects | | | |
| Yes | 18 | 18 | |
| No | 2 | 2 | |
| Previous alarm treatment | | | |
| Units: Subjects | | | |
| Yes | 10 | 10 | |
| No | 10 | 10 | |
| Weight | | | |
| Units: kilogram(s) | | | |
| arithmetic mean | 40.20 | | |
| standard deviation | ± 10.03 | - | |
| Height | | | |
| Units: centimeter | | | |
| arithmetic mean | 146.65 | | |
| standard deviation | ± 11.88 | - | |
| Percentage of nights with enuresis | | | |
| Units: percent | | | |
| arithmetic mean | 88.57 | | |

| | | | |
|--|---------|---|--|
| standard deviation | ± 15.96 | - | |
| Nocturnal urine production/expected bladder capacity | | | |
| Units: percent | | | |
| arithmetic mean | 124.49 | | |
| standard deviation | ± 54.16 | - | |
| Maximal voided volume/Expected bladder capacity | | | |
| Units: percent | | | |
| arithmetic mean | 74.70 | | |
| standard deviation | ± 26.49 | - | |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | Melatonin (Circadin, Neurim 2mg) |
| Reporting group description: Subjects receives treatment with Melatonin (Circadin, Neurim 2mg) every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received treatment with placebo every evening for four weeks. Study design was cross over. So subjects were randomized to treatment start with either melatonin or placebo for four weeks, then one week of wash out, and finally four weeks of the treatment they did not receive initially. | |

Primary: frequency of nights with enuresis

| | |
|---|-----------------------------------|
| End point title | frequency of nights with enuresis |
| End point description: | |
| End point type | Primary |
| End point timeframe: registered for each night during the course of four weeks allocated treatment , and the same procedure after cross over to the other treatment allocation | |

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 81.39 (± 25.68) | 80.82 (± 26.46) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Melatonin (Circadin, Neurim 2mg) v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.57 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.14 |
| upper limit | 6.29 |
| Variability estimate | Standard deviation |
| Dispersion value | 11.49 |

Secondary: Nocturnal urine production on enuretic nights

| | |
|-----------------|---|
| End point title | Nocturnal urine production on enuretic nights |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

registered for each night during the last week of allocated treatment , and the same procedure after cross over to the other treatment allocation

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 356 (± 109) | 355 (± 106) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Melatonin (Circadin, Neurim 2mg) v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.95 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -28.78 |
| upper limit | 30.4 |
| Variability estimate | Standard deviation |
| Dispersion value | 55.52 |

Secondary: Adherence to treatment

| | |
|-----------------|------------------------|
| End point title | Adherence to treatment |
|-----------------|------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Same as for the primary endpoint of enuresis frequency:
(registered for each night during the course of four weeks allocated treatment , and the same procedure after cross over to the other treatment allocation)

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 97.0 (± 4.4) | 96.9 (± 3.3) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Melatonin (Circadin, Neurim 2mg) v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.92 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 2.4 |
| Variability estimate | Standard deviation |
| Dispersion value | 4.6 |

Secondary: Maximal voided volume (MVV)

| | |
|-----------------|-----------------------------|
| End point title | Maximal voided volume (MVV) |
|-----------------|-----------------------------|

End point description:

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| registered each urine output for two days during the last week of allocated treatment, the largest was considered as the MVV(excluding first morning void). The same procedure after cross over to the other treatment allocation | |

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 219.8 (± 105.8) | 235.7 (± 95.8) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Placebo v Melatonin (Circadin, Neurim 2mg) |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.42 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -15.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -57.1 |
| upper limit | 25.3 |
| Variability estimate | Standard deviation |
| Dispersion value | 71.4 |

Secondary: Daytime fluid intake

| | |
|---|----------------------|
| End point title | Daytime fluid intake |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Same period as for secondary endpoint MVV | |

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 1100 (± 545) | 1216 (± 411) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Melatonin (Circadin, Neurim 2mg) v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.23 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -117 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -315 |
| upper limit | 81 |
| Variability estimate | Standard deviation |
| Dispersion value | 344 |

Secondary: Daytime urine output

| | |
|---|----------------------|
| End point title | Daytime urine output |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Same period as for secondary endpoint MVV | |

| End point values | Melatonin (Circadin, Neurim 2mg) | Placebo | | |
|--------------------------------------|--|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 18 | | |
| Units: millilitre(s) | | | | |
| arithmetic mean (standard deviation) | 804 (± 531) | 876 (± 362) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | paired t-test |
| Comparison groups | Melatonin (Circadin, Neurim 2mg) v Placebo |
| Number of subjects included in analysis | 36 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.47 |
| Method | t-test, 2-sided |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -288 |
| upper limit | 144 |
| Variability estimate | Standard deviation |
| Dispersion value | 302 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Systematically during the trial after each treatment period.

No systematic registration after trial participation.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|----------------------|
| Dictionary name | Own basic dictionary |
|-----------------|----------------------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Melatonin (Circadin, Neurim 2mg) |
|-----------------------|----------------------------------|

Reporting group description:

Adverse event during treatment with melatonin

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Adverse event during treatment with placebo

| Serious adverse events | Melatonin (Circadin, Neurim 2mg) | Placebo | |
|---|----------------------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 18 (0.00%) | 0 / 18 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Melatonin (Circadin, Neurim 2mg) | Placebo | |
|---|---|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 18 (27.78%) | 3 / 18 (16.67%) | |
| Nervous system disorders | | | |
| Headache | Additional description: headache for two days, treated with paracetamol | | |
| subjects affected / exposed | 5 / 18 (27.78%) | 3 / 18 (16.67%) | |
| occurrences (all) | 0 | 1 | |
| Tiredness | Additional description: Tiredness during daytime. Tiredness in evening shortly after ingestion of studytreatment not included | | |
| subjects affected / exposed | 5 / 18 (27.78%) | 3 / 18 (16.67%) | |
| occurrences (all) | 3 | 1 | |
| Insomnia | Additional description: Harder to fall asleep in the evening for two days | | |

| | | | |
|--|---|----------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 18 (27.78%) 0 | 3 / 18 (16.67%) 1 | |
| Gastrointestinal disorders | | | |
| Appetite disorder | Additional description: Less appetite for four days | | |
| subjects affected / exposed occurrences (all) | 5 / 18 (27.78%) 1 | 3 / 18 (16.67%) 0 | |
| Constipation | Additional description: mild for two weeks | | |
| subjects affected / exposed occurrences (all) | 5 / 18 (27.78%) 1 | 3 / 18 (16.67%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|--|--------------|
| 01 October 2014 | Lack of resources for personnel to run the trial | 02 July 2018 |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

-Early termination leads to small number of subjects for statistical analysis.
-Technical problems with armbands leading to a big amount of missing data for the following endpoints: activity, skin temperature, galvanic skin response. Data not shown

Notes: